REMARKS/ARGUMENTS

With entry of this amendment, claims 1, 6, 7, 10-12 and 29, 30, and 37-40 are pending in the above-identified application. Claim 1 is amended as set forth herein. No new matter has been added. Applicants reserve the right to pursue claims of original scope in a related, co-pending application. In view of the remarks and amendments set forth herein, reconsideration of all pending claims is respectfully requested.

Interview Summary

Applicants thank the Examiner for the teleconference of August 25, 2006, with the undersigned, during which enablement and written description issues pertaining to *in vivo* use of glycosyltransferase inhibitors and the submission of proofs relating thereto were discussed. The present response serves to enter these proofs, together with additional argument, further demonstrating enablement and written description of the pending claims. While no specific agreement was reached, the Examiner indicated that the remaining rejections would be reconsidered in light of Applicants' evidentiary submission.

Claim rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 1, 6, 7, 10-12, 29, 30 and 37-40 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not complying with the written description requirement under 35 U.S.C. § 112, first paragraph. The Examiner's primary basis for maintaining this rejection is the assertion that the application does "not adequately describe the broad genus comprising *ST3Gal-IV substrate analogs* which effectively inhibit ST3Gal-IV sialyltransferase activity in an animal and provide for the treatment effects claimed." (Office Action dated 3/6/2006 at p. 3, 2nd full para.; emphasis original.) Specifically, the Examiner appears to accept that ST3Gal-IV substrate analogs with *in vitro* inhibitory activity were known, but contends that the application and art are "silent" regarding the ability to use a representative number of such inhibitors *in vivo*, with

corresponding treatment effects. (*See id.*) Furthermore, the Examiner, while accepting that other glycosyltransferase substrate analogs have been used successfully *in vivo* (*e.g.*, tunicamycin), the Examiner states that such *in vivo* success is not "representative of the genus claimed," which is "drawn to *ST3Gal-IV substrate analogs* which effectively inhibit ST3Gal-IV sialytransferase activity in an animal and provide for the treatment effects claimed." (*Id.* at p. 4, 1st full para.; emphasis original.) The Examiner asserts that the specification provides "no guidance of what structural features are common" to previously used glycosyltransferase substrate analogs and the ST3Gal-IV substrate analogs as presently claimed. (*See id.* at p. 4, last para.) Applicants traverse the instant rejection as set forth below.

It is noted that the Examiner appears to accept Applicants' possession of ST3Gal-IV substrate analogs having *in vitro* inhibitory activity. (*See* Office Action dated 3/6/06 at p. 3, last para.) The Examiner also does not challenge the specification's demonstration that *in vivo* inhibition of ST3Gal-IV sialyltransferase would lead to a decrease in levels of vWF or FVIII in an animal, as presently claimed, and indeed the Office appears to acknowledge this biological effect of *in vivo* inhibition of ST3Gal-IV activity, as taught by the present application. (*See, e.g.*, Office Action dated 9/7/05 at pp. 24 & 25; *see also* Office Action dated 3/6/06 at p. 6.) Instead, the only issue at hand is whether one of skill in the art would reasonably accept Applicants' possession of ST3Gal-IV sialyltransferase substrate analog inhibitors having sufficient *in vivo* activity so as to achieve the claimed effects upon administration to an animal. For the reasons set forth further herein, in view of the specification's disclosure and the state of the art as of the effective filing date, the skilled artisan would indeed accept Applicants' possession of such ST3Gal-IV inhibitors having the requisite *in vivo* activity.

First, Applicants note that the desired animal target cells in the instant case are endothelial cells, which are present on the luminal surface of blood vessels. (*See* specification at, *e.g.*, p. 37, l. 28 bridging to p. 38, l. 8.) Accordingly, because the target cells are accessible via the bloodstream, the *in vivo* targets for ST3Gal-IV inhibition are readily accessible by known methods for systemic administration of pharmaceutical agents, including, *e.g.*, by intravenous administration or absorption through the gut. Once present in the bloodstream, inhibitors having the ability to passively cross cellular membranes would be expected by the skilled artisan to

passively diffuse into target endothelial cells and into the appropriate subcellular organelle to exert a corresponding physiological effect.

In light of the accessibility of the *in vivo* cellular target for ST3Gal-IV inhibition as discussed above, the skilled artisan would understand that if ST3Gal-IV inhibitors can predictably enter into cells, such as by passive diffusion, then such inhibitors could be used effectively *in vivo* in accordance with the invention as presently claimed. In this regard, it was well-known as of the effective filing date that small molecules can predictably penetrate cellular membranes, including biological membrane barriers such as the epithelial layer of the intestine, by passive diffusion. (*See, e.g.*, Camenisch *et al.*, *Eur. J. Pharm. Sci.* 6:317-24, 1998 (attached hereto as Exhibit A; in particular, *see, e.g.*, p. 313, cols. 1 & 2).) The ability of a particular small molecule to penetrate a cellular membrane by passive diffusion could be readily predicted based simply on the compound's lipophilicity and molecular size. (*See id.* at p. 313, Abstract.) Moreover, as stated by Camenisch *et al.*, "[p]assive diffusion is the most significant transport mechanism of the majority of drugs." (*Id.* at p. 313, col. 2, 1st full para.)

Thus, in light of this state of the art as evidenced by Camenisch *et al.*, the skilled artisan would reasonably accept that Applicants were in possession of ST3Gal-IV substrate analog inhibitors having *in vivo* activity. The skilled artisan would view passive diffusion across cellular membranes as indicative of a compound's ability to be absorbed and to reach its site of action. Further, it would have been predictable to determine which ST3Gal-IV inhibitors having *in vitro* activity could cross cellular membranes (*e.g.*, via the computational method of Camenisch *et al.*) Once delivered to the bloodstream, the skilled artisan would reasonably accept that such ST3Gal-IV inhibitors would predictably enter into target endothelial cells to exert a biological effect.

As an exemplary demonstration of the ability of glycosyltransferase substrate analogs to enter the Golgi region and exert specific inhibitory effects on animal cells, Applicants have attached hereto Exhibit B (Morin *et al.*, *J. Cell. Physiol.* 114:162-172, 1983, hereinafter "Morin *et al.*"), which describes the effects of tunicamycin, an inhibitor of dolichol-linked oligosaccharide synthesis, in leukemic L1210 cells. As the Examiner is aware, tunicamycin is an

inhibitor of N-acetylglucosaminyltransferase and is an analog of UDP-GlcNAc, the donor substrate for this glycosyltransferase. As described in Morin *et al.*, tunicamycin was found to specifically inhibit the incorporation of a number of sugars into glycoproteins in L1210 leukemia cells. (Morin *et al.* at Abstract; *see also* p. 164, 2nd col., 1st full para.)

Applicants believe that Morin *et al.* supports Applicants possession of *in vivo* use of ST3Gal-VI sialyltransferase inhibitors as presently claimed. As discussed above, targeting to endothelial cells via the bloodstream is already believed predictable in view of Camenisch *et al.*, which demonstrates the ability to determine passive diffusion of small molecules based on readily available physical parameters. Morin *et al.* provides particular confirmation that glycosyltransferase substrate analogs can enter into intact cells to exert specific inhibitory effects. Moreover, because Morin's L1210 luekemia cells are derived from mammalian cells, these cells are reasonably representative of the type of cells targeted in accordance with the present invention. Therefore, Applicants again submit that, once present in the bloodstream, glycosyltransferase substrate analogs having the ability to passively cross cellular membranes would be expected to enter into target endothelial cells (accessible via the bloodstream) and into the Golgi region to exert a physiological effect.

To further show that *in vivo* efficacy of glycosyltransferase inhibitors can be predictably achieved, and hence further show Applicants' possession of ST3Gal-IV sialyltransferase inhibitors with *in vivo* efficacy, Applicants refer the Examiner to Exhibit C (Kijima-Suda *et al.*, *Cancer Research* 46:858-862, 1986, hereinafter "Kijima-Suda"). Kijima-Suda describes the inhibition of blood-borne tumor cell metastasis *in vivo* upon i.v. administration of a sialyltransferase substrate analog inhibitor, KI-8110. As discussed in this reference, KI-8110 is a sialic acid:nucleoside conjugate having sialyltransferase inhibiting activity that specifically depends on the acceptor. (*See id.* at p. 860, 2nd col., 1st full para.) KI-8110 was used in Kijima-Suda's studies as a means for inhibiting sialylation of the tumor cell surface, which had been correlated to metastatic potential. (*See id.* at p. 858 (Abstract and Introduction).) Inhibition of tumor cell metastasis in mice, as well as prolongation of survival, were observed when NL-17 or NL-44 tumor cells were intravenously injected into mice, followed by injection of KI-8110. (*See id.* at Abstract; p. 859, 1st col., last para., and 2nd col.,

last para.) This effect was observed even without *in vitro* pretreatment of the NL-17 or NL-44 cells with KI-8110 (*i.e.*, where the tumor cells were exposed to the inhibitor only *in vivo*.)

For the reasons above, in addition to reasons previously of record, Applicants submit that one of skill in the art, reading the specification in light of the state of the art, would reasonably accept Applicants' possession of ST3Gal-IV sialyltransferase inhibitors having *in vivo* activity as presently claimed. Applicants' possession of ST3Gal-IV substrate analogs having *in vitro* inhibitory activity is not disputed, nor is Applicants' demonstration that *in vivo* inhibition of ST3Gal-IV would have the claimed in vivo effect, namely, a decrease in levels of vWF or FVIII in an animal. Further, it was known that the ability of a small molecule inhibitor to penetrate biological membranes could be predicted based on known physiochemical parameters, as evidenced by Camenisch *et al.* Still further, it was known as of the application's effective filing date that glycosyltransferase substrate analog inhibitors could be used successfully on animal cells, including *in vivo*, to obtain corresponding physiological effects, as evidenced by Morin *et al.* and Kijima-Suda *et al.* Accordingly, in view of the application's teachings, those skilled in the art would view the use of this general class of molecules for decreasing vWF or FVIII, by *in vivo* competitive inhibition of ST3Gal-IV sialyltransferase, to be predictable and within Applicants' possession.

In light of the above, Applicants believe claims 1, 6, 7, 10-12, 29, 30 and 37-40 to comply with the written description requirement under 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectfully requested.

Enablement

Claims 1, 6, 7, 10-12, 29, 30 and 37-40 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. The Examiner's reasons for maintaining this rejection parallel those set forth for alleging lack of written description. In particular, the Examiner accepts that the specification is enabling for *in vitro* inhibition of ST3Gal-IV sialyltransferase activity upon administration of ST3Gal-IV substrate analog inhibitors. (*See* Office Action dated 3/6/06 at p. 5.) The Examiner, however, contends that unpredictability lies

"in the undue experimentation required to deliver adequate amounts of known ST3Gal-IV substrate analogs to the proper target cells (and appropriate subcellular organelles) harboring the ST3Gal-IV sialyltransferase." (*Id.* at p. 6.) While generally accepting the specification's teachings as to the effects of ST3Gal-IV inhibition *in vivo*, the Examiner states that the "phenotypes observed upon ablation of ST3Gal-IV sialyltransferase in mice is not representative or correlative of the ability to effectively deliver ST3Gal-IV substrate analogs to an organism" so as to achieve the effects as claimed. (*Id.*) Applicants traverse the instant rejection as set forth below.

In light of the Examiner's acceptance of enablement for ST3Gal-IV substrate analog inhibitors having *in vitro* activity, as well as the Examiner's acceptance of the effects of *in vivo* ST3Gal-IV inhibition as taught in the specification, the sole issue with regard to enablement of the present claims is whether the use of ST3Gal-IV substrate analog inhibitors could be used in the context of the present invention to predictably achieve effective ST3Gal-IV inhibition *in vivo*. For the reasons set forth further herein, in view of the specification's disclosure and the state of the art as of the effective filing date, the skilled artisan would accept that inhibition of ST3Gal-IV could be predictably achieved *in vivo* to achieve the claimed treatment effects.

Initially, Applicants wish to address the Examiner's statement that Applicant "admits that it is unclear which sialyltransferase is responsible for the transfer of the terminal vWF sialic acids." (Office Action dated 3/6/06 at p. 6, citing to p. 3 of the instant specification, PCT/US00/26550.) Applicants note that the cited passage of the specification discusses previous studies regarding sialylation of vWF/FVIII. Applicants' comment therein regarding the lack of identification of specific sialyltransferases, responsible for vWF/FVIII sialyltation *in vivo*, is directed at these previous studies. The present invention adresses, *inter alia*, this previous lack of knowledge in the art by demonstrating the involvement of a specific sialyltransferase, ST3Gal-IV, in vWF/FVIII sialylation *in vivo*.

Second, with respect to the Examiner's concern regarding targeting of ST3Gal-IV substrate analog inhibitors to the proper target cells, Applicants again note that the desired animal target cells in the instant case are endothelial cells, which are present on the luminal

surface of blood vessels. (*See* specification at, *e.g.*, p. 37, l. 28 bridging to p. 38, l. 8.) As previously discussed in the context of written description, because the target cells are accessible via the bloodstream, the *in vivo* targets for ST3Gal-IV inhibition are readily accessible by known methods for systemic administration of pharmaceutical agents, including, *e.g.*, by intravenous administration or absorption through the gut. Once present in the bloodstream, inhibitors having the ability to passively cross cellular membranes would be expected by the skilled artisan to passively diffuse into target endothelial cells and into the appropriate subcellular organelle to exert a corresponding physiological effect.

Further, in view of this *in vivo* accessibility of ST3Gal-IV cellular targets, the skilled artisan would understand that if ST3Gal-IV inhibitors can predictably enter into cells, such as by passive diffusion, then such inhibitors could be used effectively *in vivo* in accordance with the invention as presently claimed. As evidenced by Camenisch *et al.* (Exhibit A), it was well-known that small molecules can predictably penetrate cellular membranes, including biological membrane barriers such as the epithelial layer of the intestine, by passive diffusion, based on readily determinable physiochemical properties such as lipophilicity and molecular size. (*See* Camenisch *et al.* at p. 313, Abstract.) Camenisch *et al.* also state that "[p]assive diffusion is the most significant transport mechanism of the majority of drugs." (*Id.* at p. 313, col. 2, 1st full para.)

In light of this state of the art as summarize above, coupled with the teachings of the instant specification, the skilled artisan would be able to determine which ST3Gal-IV substrate analog-type inhibitors can be used *in vivo* in accordance with the claimed methods without undue experimentation. The skilled artisan would understand that passive diffusion of a compound across cellular membranes, and consequently a compound's ability to be absorbed and to reach its site of action *in vivo*, is predictable, such as, *e.g.*, via the computational method of Camenisch *et al.* Thus, it would have been predictable to determine which ST3Gal-IV inhibitors having *in vitro* activity could cross cellular membranes and, once delivered to the bloodstream, the skilled artisan would reasonably accept that such ST3Gal-IV inhibitors would predictably enter into target endothelial cells to exert a biological effect.

To address the Examiner's concern regarding targeting to the appropriate subcellular organelle, a demonstration of a substrate analog's ability to specifically inhibit glycosylation in intact cells, whether in vitro or *in vivo*, demonstrates the ability of the inhibitor to enter the cell and the subcellular organelle where the target enzyme is present. Glycosyltransferases, as a class of enzymes and including ST3Gal-IV sialyltransferase, reside and exert their effects primarily in the Golgi apparatus. Therefore, Applicants further submit that the ability of a glycosyltransferase substrate analog to exert specific inhibitory effects on intact cells evidences the predictability of targeting ST3Gal-IV sialyltransferase inhibitors to the Golgi region to achieve corresponding biological effects.

As an exemplary demonstration of the ability of glycosyltransferase substrate analogs to enter the Golgi region and exert specific inhibitory effects on animal cells, Applicants again refer the Examiner to Morin *et al.* (Exhibit B), which describes the effects of tunicamycin, an inhibitor of dolichol-linked oligosaccharide synthesis, in leukemic L1210 cells. As previously noted, tunicamycin is an inhibitor of N-acetylglucosaminyltransferase and is an analog of UDP-GlcNAc, the donor substrate for this glycosyltransferase. As described in Morin *et al.*, tunicamycin was found to specifically inhibit the incorporation of a number of sugars into glycoproteins in L1210 leukemia cells. (Morin *et al.* at Abstract; *see also* p. 164, 2nd col., 1st full para.)

Further, as to the Examiner's concerns regarding targeting of the inhibitor to animal cells *in vivo*, and as previously indicated in Applicants' response to the written description rejection, Applicants believe that the predictability of *in vivo* targeting is also supported by Morin *et al.* As discussed above, targeting to endothelial cells via the bloodstream is already believed predictable in view of Camenisch *et al.*. Morin *et al.* provides particular confirmation that glycosyltransferase substrate analogs can enter into intact cells to exert specific inhibitory effects. Moreover, because Morin's L1210 luekemia cells are derived from mammalian cells, these cells are reasonably representative of the type of cells targeted in accordance with the present invention. Therefore, Applicants again submit that, once present in the bloodstream, ST3Gal-IV sialyltransferase substrate analog-type inhibitors having the ability to passively cross

cellular membranes would be expected to enter into target endothelial cells (accessible via the bloodstream) and into the Golgi region to exert a physiological effect.

To further show that *in vivo* efficacy of glycosyltransferase inhibitors can be predictably achieved, and hence further show that the skilled artisan would be able to carry out the claimed method without undue experimentation, Applicants again refer the Examiner to Kijima-Suda *et al.* (Exhibit C), which describes the inhibition of blood-borne tumor cell metastasis *in vivo* upon i.v. administration of a sialyltransferase substrate analog inhibitor, KI-8110. As previously noted, KI-8110 is a sialic acid:nucleoside conjugate having sialyltransferase inhibiting activity that specifically depends on the acceptor. (*See* Kijima-Suda at p. 860, 2nd col., 1st full para.) KI-8110 was used in Kijima-Suda's studies as a means for inhibiting sialylation of the tumor cell surface, which had been correlated to metastatic potential. (*See id.* at p. 858 (Abstract and Introduction).) Inhibition of tumor cell metastasis in mice, as well as prolongation of survival, were observed when NL-17 or NL-44 tumor cells were intravenously injected into mice, followed by injection of KI-8110. (*See id.* at Abstract; p. 859, 1st col., last para., and 2nd col., last para.) This effect was observed even without *in vitro* pretreatment of the NL-17 or NL-44 cells with KI-8110 (*i.e.*, where the tumor cells were exposed to the inhibitor only *in vivo*.)

For the reasons above, in addition to reasons previously of record, Applicants submit that achieving effective concentrations of ST3Gal-IV sialyltransferase inhibitors *in vivo*, so as to achieve the claimed treatment effect, to be predictable in view of the specification's teachings and the state of the art. The specification demonstrates that *in vivo* inhibition of ST3Gal-IV sialyltransferase *in vivo* would lead to a decrease in vWF or FVIII. Further, the particular class of inhibitors claimed – analogs of a glycosyltransferase substrate – has been used successfully *in vivo* for other indications. In addition to their use as antivirals and antibacterials, such inhibitors have been shown to exert physiological effects on mammalian cells, including *in vivo*. Morin *et al.* and Kijima-Suda *et al.*, for example, demonstrate that this class of inhibitors can target mammalian cells, including cells present in the bloodstream, to inhibit oligosaccharide synthesis and protein glycosylation reactions. Kijima-Suda *et al.*, in particular, shows that such inhibitors can be used *in vivo* so as to achieve specific enzyme inhibition in cells present in the

bloodstream to achieve a corresponding treatment effect. Accordingly, those skilled in the art would view the use of this class of molecules for decreasing vWF or FVIII, by *in vivo* competitive inhibition of ST3Gal-IV sialyltransferase in cells accessible via the bloodstream, to be predictable and, therefore, achievable without undue experimentation.

In light of the above, Applicants believe claims 1, 6, 7, 10-12, 29, 30, and 37-40 to be enabled by the specification as filed under 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectfully requested.

Claim rejections under 35 U.S.C. § 112, second paragraph

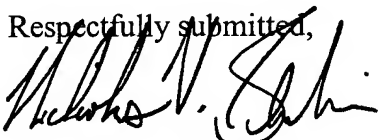
Claims 1, 6, 7, 10-12, 29, 30 and 37-40 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting "modulating" levels of vWF or FVIII in the preamble of the claim. While Applicants do not agree with the present rejection, claim 1 has been amended to substitute the term "modulating" in claim 1 with the term "decreasing." Applicants believe that this amendment obviates the present rejection under 35 U.S.C. § 112, second paragraph. Withdrawal of the rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,



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